

# PATENT COOPERATION TREATY

NIPD

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:  
OGILVY RENAULT  
1600 - 1981 McGill College Avenue  
MONTREAL, Quebec  
Canada, H3A 2Y3

21/7

**PCT**

REC'D 18 MAY 2005

PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing 11 May 2005 (11-05-2005)  
(day/month/year)

Applicant's or agent's file reference  
8426-1850PCT

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
**PCT/CA2005/000008**

International filing date (day/month/year)  
06 January 2005 (06-01-2005)

Priority date (day/month/year)  
08 January 2004 (08-01-2004)

International Patent Classification (IPC) or both national classification and IPC  
(IPC<sup>7</sup>) C07D 401/06, A61K 31/365, A61K 31/341, A61K 31/4015, A61K 31/4439, A61P 19/08, C07D 207/26, C07D 307/33

Applicant  
**MERCK FROSST CANADA & CO. ET AL**

1. This opinion contains indications relating to the following items :

- |   |              |   |
|---|--------------|---|
| <input checked="" type="checkbox"/> [X] | Box No. I    | Basis of the opinion  |
| <input type="checkbox"/> [ ]            | Box No. II   | Priority  |
| <input type="checkbox"/> [ ]            | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/> [ ]            | Box No. IV   | Lack of unity of invention  |
| <input checked="" type="checkbox"/> [X] | Box No. V    | Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement. |
| <input type="checkbox"/> [ ]            | Box No. VI   | Certain documents cited   |
| <input type="checkbox"/> [ ]            | Box No. VII  | Certain defects in the international application  |
| <input checked="" type="checkbox"/> [X] | Box No. VIII | Certain observations on the international application   |

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA  
Canadian Intellectual Property Office  
Place du Portage I, C114 - 1st Floor, Box PCT  
50 Victoria Street  
Gatineau, Quebec K1A 0C9

Facsimile No: 001(819)953-2476

Authorized officer

Irena Wisniewska (819) 953-8589

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000008

**Box No. I      Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language which it was filed, unless otherwise indicated under this item.  
  
[ ] This opinion has been established on the basis of a translation from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of :
  - a. type of material
    - [ ] a sequence listing
    - [ ] table(s) related to the sequence listing
  - b. format of material
    - [ ] in written format
    - [ ] in computer readable form
  - c. time of filing/furnishing
    - [ ] contained in the international application as filed.
    - [ ] filed together with the international application in computer readable form.
    - [ ] furnished subsequently to this Authority for the purposes of search.
3. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments :

**WRITTEN OPINION OF THE  
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International application No.  
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**Box No. V**      **Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Claims	1 - 12	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1 - 12	NO
Industrial applicability (IA)	Claims	1 - 12	YES
	Claims		NO

**2. Citations and explanations :**

Reference is made to the following documents:

D1= CA 2477657 (MERCK FROSST CANADA & CO. et al.)  
18 September, 2003 (18-09-2003)

D2= CA 2212356 (SYNPHAR LABORATORIES INC.)  
17 October, 1996 (17-10-1996)

D3= CA 2266639 (SYNPHAR LABORATORIES INC.)  
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D4= CA 2266849 (SYNPHAR LABORATORIES INC. et al.)  
26 March, 1998 (26-03-1998)

D5= Zhou, N.E. et al., "3-Acylamino-azetidin-2-one as a novel class of cysteine proteases inhibitors",  
Bioorganic & Medicinal Chemistry Letters 13 (2003) 139 - 141

**A. Novelty**

The presently claimed compounds I differ from those disclosed in D1 essentially in the fact that they possess N-terminal modification of the peptidyl or peptidomimetic molecular backbone. The presently claimed compounds I differ from those disclosed in D2 - D5 essentially in the nature of the peptidyl backbone.

Therefore, claims 1 to 12 fulfill the requirements of the PCT with respect to novelty (Article 33(2)PCT).

**B. Inventive step**

D1 - D5 relate to compounds which are cysteine protease inhibitors, including inhibitors of cathepsins. The compounds of the present application differ from those disclosed in D1 only in the modification of the N-terminal. The main basic structure (i.e. peptidyl or peptidomimetic molecular backbone) remains untouched. The structural difference merely lies in the choice of the functionality attached to the N-terminal. Documents D2 - D5 show that (optionally substituted)  $\beta$ -lactam moiety attached to peptidyl NH backbone as N-terminal play important pharmacophoric role in potency and selectivity for the papain type of cysteine proteases inhibitors. The claimed compounds of formula I possess NH -lactam terminal moiety (or its analog i.e. lactone moiety) which represent homologs and isosters of moiety disclosed in documents D2 - D5. The skilled person having a basic knowledge of the principles of structure-activity-relationships would expect the claimed compounds with such lactam or lactone terminal moieties to be cysteine protease inhibitors, including inhibitors of cathepsins. The problem underlying the present application can be regarded as to provide further compounds which inhibit cathepsins. The statement found on page 36 of the disclosure that "the compounds disclosed in the present application have an enhanced pharmacological profile relative to previously disclosed compounds" not supported by data and without specification of "previously disclosed compounds" cannot be taken for consideration. In the absence of any comparative test results between the compounds of the present application with the known compounds having the maximum structural similarity and showing unexpected or unobvious improvements, the claimed subject matter cannot be regarded as inventive.

Therefore, claims 1 to 12 do not fulfill the requirements of the PCT with respect to inventive step (Article 33(3) PCT).

**C. Industrial applicability**

The subject matter of claims 1 to 12 is considered to be industrially applicable and thus fulfilling the requirements of Article 33(4) PCT.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/CA2005/000008

**Box No. VIII      Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claims 1, 3, 5, 6 and 7 do not comply with PCT Article 6 for the following reasons: The terms "aryl", "heteroaryl", "monocyclic", "bicyclic", "haloalkyl", "keto", "alkoxy", "heterocyclyl", "hydroxyalkyl" are non-limitative and embrace an infinite number of possibilities not yet explored by the Applicant. They therefore encompass possibilities, which are not regarded as obvious modifications of the examples given which are directed to compounds of formula I wherein R<sup>3</sup> represents 2 methylpropyl optionally substituted with methyl or fluoro; E-D represents biphenyl - 4 with very specific substituents R<sup>5</sup> ; Z and Y represent CH<sub>2</sub> .

The 5<sup>th</sup> compound claimed in claim 7 (when pyrrolidinyl moiety is substituted with pyridin-2-ylmethyl) does not represent compounds of formula I as claimed in claim 1.

The description does not comply with PCT Article 5 for the following reasons:

A statement in the application, such as found on page 1, 2, 13, 14, 15, 18, 23 which incorporates by reference any other document, does not fully describe the invention. The description shall be complete in and on itself.

The Applicant should cite and briefly discuss the prior art document D1.

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